

How's My Dosing 2.0: Comparison of 2003-2011 Immunotherapy Practice Parameter Maintenance Dose Recommendations and Updated Math-Free Formulation Tables



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Abstract

Introduction

The administration of allergen extracts at maintenance immunotherapy (IT) doses known to be both effective and safe is an essential practice in allergy clinics. Practice parameters for allergen IT have been published 3 times over the last 9 years, with each update containing different target dose levels or ranges for several allergens compared to previous and most recent versions. An IT worksheet distributed by AAAAI shortly after publication of the 2003 parameters also included different dose ranges for most extract categories. These changes in IT dose guidelines reflected either new information or a broader consensus opinion among practicing allergists.

Methods

In 2006, a simple, easy-to-use set of tables ("How's My Dosing") was created to define the volumes of extract concentrates required in IT mixtures to achieve the treatment doses cited in the practice parameters, and to circumvent the need to perform multiple algebraic steps with each allergen in the mix. These tables (based on the 2004 AAAAI worksheet doses and calculations using the common conservation of mass formula $V_1C_1 = V_2C_2$) specified the exact extract volumes or vial volume percentages corresponding to delivery of the minimum, midrange and maximum dose levels within each target dose range. Because of the changes in IT dosing recommendations summarized in the subsequent 2007 and 2011 IT practice parameters, updates of the tables are warranted.

Results

A chronological summary highlights the changes in published IT dose recommendations from the various documents for each extract category. Updated IT dose tables are provided for allergens formulated in 5.0 mL final volumes with 0.5 mL injection volumes. Vial volume percentage tables are also included to facilitate formulations with 5.0 mL or any other final maintenance IT vial volume. Tables are constructed with columns defining the extract category, concentrate strength, target dose ranges and the resulting volumes or percentages needed to produce doses at the lower limit, upper limit and middle of each range.

Conclusions

These data, when combined with information on allergenic cross-reactivity, extract compatibility and glycerin tolerance, provide clinicians with a convenient and systematic method for the formulation of maintenance IT mixtures, and facilitate dosing decisions for patients exhibiting a wide variety of allergen sensitivities and specificities.

IT Doses: 2003-2011

Maintenance IT doses published in the 2004 AAAAI IT worksheet and the 2003, 2007 and 2011 IT practice parameters are tabulated below in chronological order. Changes from the previous publication are highlighted.

IT doses for standardized extracts were mostly consistent across the various updates. The changes observed for these products included a reduced upper limit (short ragweed), reduced lower limit (pasture grasses), reduced lower plus increased upper limits (cat), and clarification of dose ranges for specific products (dust mite *Dermatophagoides* species). Bermuda grass doses were reported first in 2011 to differentiate IT recommendations for this subtropical species from those of the temperate pasture grasses.

All doses are based on a 0.5 mL injection volume. Thus, to deliver a 1,000 BAU dose of cat allergen, an IT solution or mixture containing 2,000 BAU/mL of cat extract is prepared.

Extract category	Target IT doses/ranges published in ...			
	2003	2004	2007	2011
Short ragweed	6-24 AgE U (µg) 1:30-1:100 w/v	6-12 AgE U (µg) 1:50-1:250 w/v	6-12 AgE U (µg)	6-12 AgE U (µg)
Cat	2,000-3,000 BAU	2,000-3,000 BAU	1,000-4,000 BAU	1,000-4,000 BAU
Dust mites	600 or 2,000 AU	500-2,000 AU	500-2,000 AU	500-2,000 AU
Pasture grasses	4,000 BAU	1,000-4,000 BAU	1,000-4,000 BAU	1,000-4,000 BAU
Bermuda grass	Not specified	Not specified	Not specified	300-1,500 BAU

Non-standardized extract dose recommendations were also modified across these documents. Dose ranges were expanded and then narrowed (pollen), specified generically as the highest tolerated dose (HTD: fungi, insects), and reported at one dose based on a single study with an acetone-precipitated (AP) dog extract.

Extract category	Target IT doses/ranges published in ...			
	2003	2004	2007	2011
Pollen	1:30-1:100 w/v	1:50-1:250 w/v	Highest tolerated dose	1:100-1:200 w/v
Fungi	1:50-1:100 w/v	1:50-1:250 w/v	Highest tolerated dose	Highest tolerated dose
Insects	Not specified	Not specified	Highest tolerated dose	Highest tolerated dose
Dog AP	Not specified	Not specified	15 µg Can f 1	15 µg Can f 1

Pollen/Fungi/Insects

Non-standardized pollen, fungal and insect extracts are labeled in w/v strengths. Analogous products from different U.S. manufacturers can possess variable protein compositions, allergen concentrations and IgE-binding activities related to differences in source materials, extraction conditions and processing steps. All products are available in 50% glycerin. Selected products can also be obtained as non-glycerinated (aqueous) concentrates.

IT dose recommendations for these product groups have changed over time, a response to both the manufacturing issues noted above and to variations in patient sensitivity caused by qualitative or quantitative differences in allergen exposures across diverse geographic regions. Thus, the HTD for a given extract can range from very high (eg. 1:100 w/v) to moderate (eg. 1:1,000-1:2,000 w/v) or lower concentrations in different clinics and patients.

In this summary, a target dose range of 1:100-1:200 w/v has been selected for non-standardized extracts labeled in w/v units. In areas where these doses are poorly tolerated, suitable reductions of these volumes or percentages, or use of similar volumes of the previous vial strength (10-fold dilution of maintenance concentrate), should be considered.

Extract volumes needed to achieve a 1:100-1:200 w/v dose range were determined at the lower limit (Min), upper limit (Max) and middle (Mid) of this range, and are tabulated below for both 5.0 mL (top) and variable (bottom) IT vial volumes when administered at 0.5 mL injection volumes.

Extract volumes needed for 5.0 mL maintenance IT vials

Extract/Concentrate Strength		mL of concentrate needed per vial		
Category	Concentrate	Min	Mid	Max
Pollens, Fungi, Insects	1:10 w/v	0.25	0.375	0.50
	1:20 w/v	0.50	0.75	1.00
	1:40 w/v	1.00	1.50	2.00

Extract percentages (5.0 mL or variable IT vial volumes)

Extract/Concentrate Strength		% of vial volume		
Category	Concentrate	Min	Mid	Max
Pollens, Fungi, Insects	1:10 w/v	5	7.5	10
	1:20 w/v	10	15	20
	1:40 w/v	20	30	40

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Ragweed/Cat/Dog

Standardized short ragweed extracts are labeled in both w/v and major allergen Amb a 1 (Antigen E) concentrations (Units/mL, = µg/mL), with a 1:20 w/v glycerinated product averaging close to 200 AgE U/mL. The IT dose recommendation of 6-12 AgE Units for short ragweed extract has been consistent since 2004.

Standardized cat extracts are labeled in BAU/mL based on the concentrations of major allergen Fel d 1. The dose range for glycerinated cat extract was expanded in 2007 to 1,000-4,000 BAU (from 2,000-3,000 BAU).

Non-standardized dog extracts can be prepared from various source material types by different manufacturers. The single IT dose cited in 2007 and 2011 was based on a study with a glycerinated AP dog hair-dander extract containing high levels of Can f 1 but low levels of Can f 3 (albumin). Dog epithelia extracts available in both aqueous and glycerinated forms exhibit high Can f 3 and low Can f 1 levels, and are typically utilized at target doses similar to pollen, fungal and insect extracts (1:100-1:200 w/v, or HTD).

Extract volumes and percentages required to reach dose ranges of 6-12 AgE U for short ragweed, 1,000-4,000 BAU for cat, 15 µg Can f 1 for dog AP, and 1:100-1:200 w/v for dog epithelia are shown below. Ragweed mix (short + giant) volumes are similar to short ragweed alone due to the strong cross-reactivities between allergens from the two species.

Extract volumes needed for 5.0 mL maintenance IT vials

Extract/Concentrate Strength		mL of concentrate needed per vial		
Category	Concentrate	Min	Mid	Max
Short ragweed*	200 AgE U/mL	0.30	0.45	0.60
Cat	10,000 BAU/mL	1.00	2.50	4.00
Dog AP	1:100 w/v	NA	NA	1.00
Dog epithelia	1:10 w/v	0.25	0.375	0.50
	1:20 w/v	0.50	0.75	1.00

* Also applies to Ragweed mix (short + giant) products at 1:20 w/v and ~ 100 AgE U/mL.

Extract percentages (5.0 mL or variable IT vial volumes)

Extract/Concentrate Strength		% of vial volume		
Category	Concentrate	Min	Mid	Max
Short ragweed*	200 AgE U/mL	6	9	12
Cat	10,000 BAU/mL	20	50	80
Dog AP	1:100 w/v	NA	NA	20
Dog epithelia	1:10 w/v	5	7.5	10
	1:20 w/v	10	15	20

* Also applies to Ragweed mix (short + giant) products at 1:20 w/v and ~ 100 AgE U/mL.

Dust Mite/Grasses

Standardized dust mite extracts are labeled in AU/mL and are available at two strengths (30,000 and 10,000 AU/mL). A target dose range of 500-2,000 AU has been recommended for dust mites since 2004. This range represents the specific AU levels when extracts from only one species are used, or the total AU doses when both species are included.

Standardized pasture grass extracts are labeled in BAU/mL, with two concentrations available (100,000 and 10,000 BAU/mL). IT dose ranges for these grasses have also remained constant since 2004. As with the dust mites, this range reflects the total BAU doses for pasture grass mixtures and the individual grass extract dose when a single pasture grass extract representing this homologous product group is selected for IT.

Standardized Bermuda grass extracts are labeled in BAU/mL at a single concentration (10,000 BAU/mL). The lower BAU strength of Bermuda relative to pasture grasses is due to reduced Bermuda sensitivities of the subjects involved in the quantitative skin tests used to assign BAU potencies. An IT dose range of 300-1,500 BAU was first recommended for Bermuda in 2011.

The volumes of these glycerinated extracts or mixes needed to deliver dose ranges of 500-2,000 AU for dust mites, 1,000-4,000 BAU for pasture grasses and 300-1,500 BAU for Bermuda grass in 0.5 mL injections are listed below.

Extract volumes needed for 5.0 mL maintenance IT vials

Extract/Concentrate Strength		mL of concentrate needed per vial		
Category	Concentrate	Min	Mid	Max
Dust mites	30,000 AU/mL**	0.17	0.42	0.67
	10,000 AU/mL**	0.50	1.25	2.00
Pasture grasses	100,000 BAU/mL**	0.10	0.25	0.40
	10,000 BAU/mL**	1.00	2.50	4.00
Bermuda grass	10,000 BAU/mL	0.30	0.90	1.50

** Also applies to Dust mite mix and Pasture grass mix (eg. KORT, 7 grass) products at the same AU/mL or BAU/mL strengths

Extract percentages (5.0 mL or variable IT vial volumes)

Extract/Concentrate Strength		% of vial volume		
Category	Concentrate	Min	Mid	Max
Dust mites	30,000 AU/mL**	3.4	8.4	13.4
	10,000 AU/mL**	10	25	40
Pasture grasses	100,000 BAU/mL**	2	5	8
	10,000 BAU/mL**	20	50	80
Bermuda grass	10,000 BAU/mL	6	18	30

** Also applies to Dust mite mix and Pasture grass mix (eg. KORT, 7 grass) products at the same AU/mL or BAU/mL strengths

Applications

Using the Min, Mid and/or Max columns of each table, the numbers and types of extracts that can be combined into IT vaccines are determined by adding the volumes from the columns corresponding to the desired doses (or vial volume percentages), up to the total IT vial contents (5.0 mL or 100%). For example, maintenance vials can contain up to ten 1:10 w/v extracts at Max doses, or up to ten 1:20 w/v products at Min doses (0.5 mL ea. or 10% of total volume).

The final glycerin concentrations of IT mixtures can be determined easily using either the 5.0 mL or variable volume IT tables. When using the 5.0 mL tables, add the volumes of all products supplied in 50% glycerin, then multiply by 10. With the volume percentage tables, add the percentages for all glycerinated items, then divide by 2. Glycerin levels above 20-25% may be difficult to tolerate for some IT patients.

Cross-reactive allergens contribute additive doses for many patients. Selection of extract mixtures containing allergens within well-defined homologous groups may be preferred in some cases compared to utilization of a single product representative of these groups.

With knowledge of extract compatibilities, IT vaccines can be formulated into a minimal number of maintenance vials for individual patients, and are more likely to remain stable during storage at 2-8°C and short-term exposures at room temperature (20-25°C).

Non-standardized extracts at similar w/v strengths from different manufacturers may vary in composition, allergen levels, potency or glycerin content. Check with your extract provider for further information.

Conclusions

The IT dose tables presented here summarize the changes reported in recent practice parameter updates and provide clinicians with a convenient, math-free guide to analyze their current doses and/or optimize new formulations based on these recommendations.

These data, when considered with allergen cross-reactivity, extract compatibility, glycerin tolerance and other clinical judgments, can facilitate IT dosing decisions by physicians for patients presenting with a diverse range of environmental exposures, allergen sensitivities and IgE specificities.

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Stock Mixes and Glycerin Content

Allergic patients being considered for IT can display independent sensitivities to allergens from related sources, but more often exhibit moderate to high degrees of cross-reactivity with allergens from homologous organisms. Species within the same genus (or same tribe for grasses) typically display very similar extract compositions and IgE-binding properties. Some species or genera within the same family can also retain similar allergen structures or sequences. Clinicians must decide if a single representative extract is appropriate for treating these patients, or if a stock (or customized) mixture containing multiple cross-reactive extracts provides a more suitable repertoire of allergens.

Because of these cross-reactivities (and noted under several of the dose tables), when stock mixes containing extracts from the same genus (ragweed mix, dust mite mix) or same tribe (pasture grass mixes) are utilized in place of single-species products representative of these groups, equivalent extract volumes and target doses are recommended.

When using stock mixes of unrelated (non-cross-reactive) extracts, however, the allergen potencies are not additive but individualized, and represent only a fraction of the total or labeled extract strength for these products. For example, a regional pollen mix composed of 6 unrelated tree species at a labeled (total) strength of 1:20 w/v actually contains each allergen at a final strength of 1:120 w/v. Volumes of these mixes added to IT prescriptions may need to be increased accordingly to achieve therapeutic doses. In some clinics, mixes such as these are utilized as maintenance IT concentrates without further extract additions or dilution.

The glycerin concentrations of the various allergenic extract concentrates used for IT are also noted in the previous sections. When formulating maintenance IT mixtures for patients, monitoring the component and final glycerin levels is critical. Patient tolerance to the irritation effects of glycerin injections begin to decline at 15-20% glycerin, and higher levels are associated with increased pain, local reactions, and reduced adherence to treatment.

Creating optimal maintenance vial mixtures (with minimal numbers of separate vials and injections) for patients at final glycerin concentrations below 20-25% requires a balance of extract dose targets, use of aqueous extract concentrates for some allergens, and specific product combinations (with associated glycerin levels) that possess favorable allergen stability and compatibility under typical storage conditions.

Several examples of IT mixtures incorporating these vial formulation considerations and guidelines are provided.

Example 1: Pollens

For these examples, the general extract compatibility recommendation of separating protease-rich fungal and insect extracts from low-protease pollen, dust mite and dog extracts will be adopted.

In the first example, a total of 10 non-standardized pollen allergens producing positive skin tests have been selected as candidates for IT. The 10 allergens include:

- 5 trees: box elder, cottonwood, elm, maple, oak
- 2 grasses: kentucky blue, timothy
- 3 weeds: lamb's quarter, pigweed, short ragweed

First, examine the 10 allergens for known patterns of cross-reactivity. Among the 5 trees, box elder and maple belong to the same genus and are highly cross-reactive. The same is true for the 2 grasses, kentucky blue and timothy grass.

Selection of one or the other product, or a mix, is influenced in part by the product strengths and formulations available. If box elder is provided only in 50% glycerin but maple is offered in both aqueous and glycerinated forms, maple may be a better selection. If a maple-box elder mix is also offered at the same aqueous strength, it can be used at the same volumes as the maple extract (remember: cross-reactivity = additive doses in genetically-related mixes).

Both kentucky blue and timothy are available in 50% glycerin at the same BAU/mL strengths. Either product, or a grass mix containing these species (eg. KOT, KORT) can be selected. For this example, timothy alone will be used.

The 8 pollen extracts selected for this IT mixture are compatible and can be combined into a single maintenance vial. Using data from the 5.0 mL volume tables for these products, mixtures at the Min, Mid and Max dose levels are feasible and can be prepared as follows:

Extract	Concentrate	Min (mL)	Mid (mL)	Max (mL)
Cottonwood	1:10 w/v, aqueous	0.25	0.375	0.50
Elm	1:10 w/v, aqueous	0.25	0.375	0.50
Maple	1:10 w/v, aqueous	0.25	0.375	0.50
Oak	1:10 w/v, aqueous	0.25	0.375	0.50
Timothy	100K BAU/mL, 50%G	0.10	0.25	0.40
Lambs quarter	1:20 w/v, 50%G	0.50	0.75	1.00
Pigweed	1:10 w/v, aqueous	0.25	0.375	0.50
Short ragweed	200 AgE U/mL, 50%G	0.30	0.45	0.60
All allergens		2.15	3.325	4.50
Diluent (aqueous)		2.85	1.675	0.50
Glycerinated allergens		0.90	1.45	2.00
Final glycerin concentration		9.0%	14.5%	20.0%

Example 2: Diverse Allergens

In the second example, a more complex combination of 21 diverse allergens is selected for IT, including the following:

- 4 trees: cottonwood, elm, oak, poplar
- 4 grasses: KORT mix
- 4 weeds: cocklebur, nettle, short/giant ragweed mix
- 2 dust mites: D. farinae/D. pteronyssinus mix
- 3 animals: cat, dog AP, dog epithelia
- 3 fungi: Alternaria, Aspergillus, Penicillium
- 1 insect: German cockroach

Cottonwood can cover poplar based on their strong cross-reactivity. The remaining extracts are dosed independently.

Pollen and dust mite extracts possess limited compatibility with fungal and insect extracts and are added to separate IT vials. Cat extracts are stable when mixed with fungi or insects and can be added to either vial. This flexibility could circumvent the need for additional IT vials and injections.

Extract	Concentrate	Min (mL)	Mid (mL)	Max (mL)
Cottonwood	1:10 w/v, aqueous	0.25	0.375	0.50
Elm	1:10 w/v, aqueous	0.25	0.375	0.50
Oak	1:10 w/v, aqueous	0.25	0.375	0.50
KORT mix	100K BAU/mL, 50%G	0.10	0.25	0.40
Cocklebur	1:20 w/v, 50%G	0.50	0.75	1.00
Nettle	1:10 w/v, aqueous	0.25	0.375	0.50
Ragweed mix	1:20 w/v (100 AgE U/mL), 50%G	0.30	0.45	0.60
Dust mite mix	30K AU/mL, 50%G	0.17	0.42	0.67
Dog AP	1:100 w/v, 50%G	1.00	1.00	1.00
Dog epithelia	1:10 w/v, aqueous	0.25	0.375	0.50
All allergens in Vial 1		3.32	4.745	6.17*
Diluent (aqueous)		1.68	0.255	NA
Glycerinated allergens in Vial 1		2.07	2.87	3.67
Final glycerin concentration in Vial 1		20.7%	28.0%	29.7%

Extract	Concentrate	Min (mL)	Mid (mL)	Max (mL)
Alternaria	1:20 w/v, aqueous	0.50	0.75	1.00
Aspergillus	1:10 w/v, aqueous	0.25	0.375	0.50
Penicillium	1:10 w/v, aqueous	0.25	0.375	0.50
German cockroach	1:20 w/v, 50%G	0.50	0.75	1.00
Cat	10K BAU/mL, 50%G	1.00	2.50	4.00
All allergens in Vial 2		2.50	4.75	7.00*
Diluent (aqueous)		2.50	0.25	NA
Glycerinated allergens in Vial 2		1.50	3.25	5.00
Final glycerin concentration in Vial 2		15.0%	32.5%	35.7%

* Final extract doses are below target levels when total vial volumes exceed 5.0 mL, in proportion to overage volume

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How's My Dosing 2.0 Immunotherapy Formulation Tables



Extract volumes needed for 5.0 mL maintenance IT vials

Extract/Concentrate Strength		mL of concentrate needed per vial		
Category	Concentrate	Min	Mid	Max
Pollens, Fungi, Insects	1:10 w/v	0.25	0.375	0.50
	1:20 w/v	0.50	0.75	1.00
	1:40 w/v	1.00	1.50	2.00
Short ragweed*	200 AgE U/mL	0.30	0.45	0.60
Cat	10,000 BAU/mL	1.00	2.50	4.00
Dog AP	1:100 w/v	NA	NA	1.00
Dog epithelia	1:10 w/v	0.25	0.375	0.50
	1:20 w/v	0.50	0.75	1.00
Dust mites	30,000 AU/mL**	0.17	0.42	0.67
	10,000 AU/mL**	0.50	1.25	2.00
Pasture grasses	100,000 BAU/mL**	0.10	0.25	0.40
	10,000 BAU/mL**	1.00	2.50	4.00
Bermuda grass	10,000 BAU/mL	0.30	0.90	1.50

* Also applies to Ragweed mix (short + giant) products at 1:20 w/v and ~ 100 AgE U/mL

** Also applies to Dust mite mix and Pasture grass mix (eg. KORT, 7 grass) products at the same AU/mL or BAU/mL strengths

Extract percentages (5.0 mL or variable IT vial volumes)

Extract/Concentrate Strength		% of vial volume		
Category	Concentrate	Min	Mid	Max
Pollens, Fungi, Insects	1:10 w/v	5	7.5	10
	1:20 w/v	10	15	20
	1:40 w/v	20	30	40
Short ragweed*	200 AgE U/mL	6	9	12
Cat	10,000 BAU/mL	20	50	80
Dog AP	1:100 w/v	NA	NA	20
Dog epithelia	1:10 w/v	5	7.5	10
	1:20 w/v	10	15	20
Dust mites	30,000 AU/mL**	3.4	8.4	13.4
	10,000 AU/mL**	10	25	40
Pasture grasses	100,000 BAU/mL**	2	5	8
	10,000 BAU/mL**	20	50	80
Bermuda grass	10,000 BAU/mL	6	18	30

* Also applies to Ragweed mix (short + giant) products at 1:20 w/v and ~ 100 AgE U/mL

** Also applies to Dust mite mix and Pasture grass mix (eg. KORT, 7 grass) products at the same AU/mL or BAU/mL strengths

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